II. RESPONSE

A. Status of the Claims

The Action withdrew the restriction requirement between Groups I and IV. Thus, claims 67-69 and 73 were examined in the Action. New claim 98-103 have been added. Thus, claims 67-69, 73, and 98-103 are currently pending. Support for the new claims can be found in the specification at, for example, page 9, lines 19-22; page 11, lines 1-4; page 40, lines 18-20; and page 7, ln. 27 to page 8, line 3.

B. The Claims Satisfy the Written Description Requirement

The Action rejects claims 67-69 and 73 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Action notes that the specification describes the complete structure of mouse and rat ACE2. The Action asserts, however, that the skilled artisan could not predict the structure of any other ACE2 activator nor could a skilled artisan predict the structure of any domain or unique sequence in all different species. Applicant traverses this rejection.

In rejecting a claim under the written description requirement, the Action is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, Paragraph 1.* It appears, however, that in making the present written description rejection, the Examiner did not apply the proper legal standard and overlooked substantial portions of the disclosure in the specification.

With regard to the legal standard issue, the Action improperly concludes that the specification does not provide adequate written description because it does not convey to one skilled in the art that Applicant was in possession of **all** the different ACE2 activators effective in

mammals (Action, p. 5). This is not the proper legal analysis for evaluating the written description requirement. The written description requirement for a claimed genus may be satisfied through sufficient description of a **representative number** of species. It is not necessary that every permutation within a generally operable invention be effective for Applicant to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

With regard to the disclosure in the present specification, Applicant would first like to point out that, in addition to mouse and rat ACE2 nucleic acid sequence, the present specification also discloses the complete structure of human ACE2 (*see e.g.*, SEQ ID NOs. 1 and 2; and FIG. 1A) as well as the amino acid sequences of mouse and rat ACE2 (*see e.g.*, FIG. 1A). This appears to have been overlooked by the Examiner. Furthermore, in asserting that the only identifying characteristics of the ACE2 sequence provided in the specification is that it antagonizes RAS and heart failure (Action, p. 4), it appears that the Examiner also overlooked several other passages in the specification. As described below, the currently claimed genus is supported by sufficient description of the relevant, identifying characteristics, of a representative number of species.

For example, FIG. 1A in the present specification provides an alignment of the amino acid sequences of ACE2 from human, rat, and mouse, which illustrates the identities and similarities between these sequences. In addition, results in flies showed that a P-element mutation associated with the ACE homologue, ACER, results in a severe and lethal defect of heart morphogenesis providing further evidence that ACE/ACE2 functions in the heart have been conserved through evolution (Specification, p. 30, ln. 28 to p. 31, ln. 2). As further evidence of the conservation of the ACE/ACE2 system, Applicant encloses a publication entitled "Structure,

Evolutionary Conservation, and Function of Angiotensin- and Endothelin-Converting Enzymes" (Macours *et al.*, *International Review of Cytology*, 239:47-97 (2004)). In addition, the enclosed BLAST search of the ACE2 substrate, AngII, shows that AngII is present in numerous mammals including *Pan troglodytes, Mus musculus, Homo sapiens, Callithrix jacchus, Gorilla gorilla, Canis familiearis, Macaca mulatta, Rattus norvegicus, Ovis ammon,* and *Pongo pygmaeus.* In view of the similarities of the rat, mouse, and human ACE2 sequence and the presence of ACE2 substrate in numerous organisms, those of ordinary skill in the art would understand that the claimed method could be performed in a multitude of mammals and in humans.

FIG. 1B is a schematic representation of ACE and ACE2 in which (1) the zinc binding site, (2) the catalytic center, (3) the signal peptide, and (4) the transmembrane domain are identified. Furthermore, the specification discloses that AngI and AngII are substrates for ACE2, which functions as a carboxypeptidase to cleave a single residue from each of AngI and AngII (p. 2, ln. 5-10). The specification also discloses the expression pattern of ACE2 (p. 2, ln. 3-5) and that ACE2 inhibitors are known in the art (p. 2, ln. 15-17). Thus, the present specification discloses: (1) ACE2 structure; (2) ACE2 function; (3) a known correlation between ACE2 structure and function; and (4) that ACE2 has been conserved through evolution. Applicant further notes that the structure of human ACE2 was also provided in the Acton patents (U.S. Patents 6,194,556 and 6,632,830) cited in the Action (*see e.g.*, '556 patent, col. 3, ln. 4-43; '830 patent, col. 4, ln. 46 to col. 5, ln. 38).

Moreover, the animal model studies in the present specification demonstrate that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases. Accordingly, those of ordinary skill in the art would have appreciated the therapeutic benefit of administering an ACE2 agonist based on the disclosure in the present specification. Furthermore, those of

ordinary skill in the art would understand that the specification adequately describes numerous such agonists. For example, the specification discloses ACE2 nucleic acid molecules and ACE2 polypeptides as an ACE2 agonist (*see e.g.*, p. 10, ln. 10 to p. 13, ln. 27). In addition, the specification discloses that compounds that bind ACE2 may also be useful as agonists (Specification, p. 15, ln. 8-13).

The enclosed reference by Imai *et al.* (*Nature*, 436:112-116 (2005) is further evidence that the present specification's disclosed *in vivo* role of ACE2 in the regulation of the renin-angiotensin system is correct and would have been understood by a person of ordinary skill in the art. Applicant also encloses a reference by Kuba *et al.* (*Nature Medicine*, 11:875-879 (2005)) as further evidence that lung injury is an ACE2 decreased state (*see e.g.*, p. 875, col. 2, second paragraph). Imai *et al.* reported that ACE2 protected mice from severe acute lung injury, whereas other renin-angiotensin components such as ACE and AngII induced lung edemas and impaired lung repair (*see* Abstract). As shown in Figures 2(d)-(f) of Imai *et al.*, treatment of ACE2 knock-out mice with a recombinant human ACE2 protein, an ACE2 activator, resulted in the attenuation of lung injury. These results provide further support that ACE2 functions as a negative regulator of the renin-angiotensin system and, therefore, that an ACE2 activator should be used to treat an ACE2 decreased state such as lung injury. This is in contrast to role of ACE2 predicted by the Acton patents and the consequent teaching by Acton that an ACE2 antagonist would be the appropriate therapy (*see* discussion in Section C below). The results of Imai *et al.* also provide additional evidence of the conserved function of ACE2 and the renin-angiotensin system by virtue of the fact that a human ACE2 protein was able to complement ACE2 function in ACE2 knock-out mice.

In view of the disclosure of three mammalian ACE2 sequences, the evolutionary conservation of ACE2 structure and activity, ACE2 function, and a correlation between ACE2 structure and function, a person of ordinary skill in the art can reasonably concluded that Applicant had possession of a representative number of ACE2 agonists including, ACE2 nucleic acids, ACE2 polypeptides, and molecules that bind ACE2 domains and sequences, at the time of filing.

In view of the above, Applicant submits that the present specification describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that Applicant had possession of the claimed invention at the time of filing. Applicant, therefore, requests the withdrawal of this rejection.

C. The Claims Are Novel Over the Cited Art

1. U.S. Patent 6,194,556

The Action rejects claims 67-68 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 6,194,556 (the '556 patent). Applicant traverses this rejection.

The '556 patent discloses that because of its homology to ACE, ACE2 is likely to hydrolyze AngI into AngII, which is a vasoconstrictor ('556 patent, col. 56, ln. 19-39). Thus, the '556 patent predicts that ACE2 ***antagonists*** would be useful in treating hypertension (Id.; *see also* col. 57, ln. 10-20). This is contrast to the disclosure in the present specification, which provides a different paradigm for the regulation of the renin-angiotension system. The present specification discloses that hypertension, as well as other cardiac, lung, and kidney diseases are the result of an ACE2 decreased state (*see e.g.*, p. 2, ln. 28 to p. 3, ln. 6). The present specification, therefore, discloses the use of an ACE2 ***activator*** for treating hypertension, as well as other cardiac, lung, and kidney diseases. It appears that the only therapeutic uses of an ACE2

activator contemplated by the '556 patent are for the treatment of inflammation, burns, and insect bites, which are not ACE2 decreased states ('556 patent, col. 58, ln. 7, ln. 51-54).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. As set forth above, the '556 patent does not teach a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of an ACE2 activator. The '556 patent actually teaches a person of ordinary skill in the art the opposite (*i.e.,* administering an ACE2 antagonist when an ACE2 activator is needed) of the currently claimed invention. A claim cannot be anticipated by a reference if the allegedly anticipatory disclosure is not enabled. Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. MPEP § 2101.01. Because the '556 patent's predicted mechanism for *in vivo* ACE2 activity was incorrect, a person of ordinary skill in the art would not have been able to practice the currently claimed invention based on the teachings of the '556 patent without undue experimentation.

In view of the above, claims 67-68 are novel over the '556 patent. Applicant, therefore, requests the withdrawal of this rejection.

2. U.S. Patent 6,632,830

The Action rejects claims 67-68 and 73 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 6,632,830 ('830 patent). Applicant traverses this rejection.

Like the '556 patent, the '830 patent discloses that because of its homology to ACE, ACE2 is likely to hydrolyze AngI into AngII, which is a vasoconstrictor ('830 patent, col. 35, ln. 27-38). Thus, the '830 patent also predicts that ACE2 ***antagonists*** would be useful in treating hypertension (Id.). Accordingly, the '830 patent does not teach a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a

therapeutically effective amount of an ACE2 activator. The '830 patent actually teaches a person of ordinary skill in the art the opposite (*i.e.,* administering an ACE2 antagonist when an ACE2 activator is needed) of the currently claimed invention.

With regard to claim 73, the Action asserts that the '830 patent contemplates a method of treating CHF by administering ACE inhibitory compounds concurrently with an ACE2 modulating compound (Action, p. 7, citing '830 patent, col. 35, ln. 30-32). However, if one reads the complete paragraph in the '830 patent, it can be seen that the ACE2 modulating compound is an ACE2 inhibiting compound ('830 patent, col. 35, ln. 29-38). As mentioned above, the '830 patent incorrectly predicted the *in vivo* mechanism for ACE2 activity and, therefore, teaches a person of ordinary skill in the art to do the opposite (*i.e.,* administer an ACE2 antagonist when an ACE2 activator is needed) of the currently claimed invention.

A claim cannot be anticipated by a reference if the allegedly anticipatory disclosure is not enabled. Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. MPEP § 2101.01. Because the '830 patent's predicted mechanism for *in vivo* ACE2 activity was incorrect, a person of ordinary skill in the art would not have been able to practice the currently claimed invention based on the teachings of the '830 patent without undue experimentation.

In view of the above, claims 67-68 and 73 are novel over the '830 patent. Applicant, therefore, requests the withdrawal of this rejection.

D. The Claims Are Patentable Over the Cited Art

The Action rejects claims 67-69 and 73 under 35 U.S.C. § 103(a) as being unpatentable of the '830 patent in view of Crackower *et al.* The Action notes that the '830 patent does not specifically teach administering an ACE2 activator/agonist for the treatment of ACE2 decreased state associated hypertension and, in fact, teaches contrary to the instantly recited claim (Action,

p. 9). The Action asserts that Crackower discloses that reduced ACE2 activity increases hypertension. Thus, the Action asserts that it would have been obvious to modify the '830 patent's methods of treating ACE2 associated disorders in a manner contrary to its teachings in view of the disclosure in Crackower. Applicant traverses this rejection.

When an obviousness determination is based on multiple prior art references, there must be a showing of some "teaching, suggestion, or reason" to combine the references. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579 (Fed. Cir. 1997) (also noting that the "absence of such a suggestion to combine is dispositive in an obviousness determination"). The Action has failed to establish such a motivation to combine the '830 patent and Crackower. The Action concedes that the '830 patent teaches a method that is contrary to the currently claimed method. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness. *In re Gurley*, 27 F.3d 551, 554 (Fed. Cir. 1994).

Furthermore, if the proposed modification or combination of the cited art would change the principle of operation of the method being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious (MPEP § 2143.01(VI)). The Action's suggested modification of the method of the '830 patent would require a complete revision of the principle of operation set forth in the '830 patent in that the suggested modification would require one to use an ACE2 activator/agonist when the '830 patent teaches the use of an ACE2 antagonist. Such a modification is not *prima facie* obvious (*see* MPEP § 2143.01(VI)).

For the reasons above, the claims are patentable over the cited references. Applicant, therefore, requests the withdrawal of the rejection.

E. Conclusion

In view of the above, Applicants believe that they have submitted a complete reply to the Office Action dated March 8, 2006. Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicant's representative at (512) 536-5654.

Respectfully submitted,

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